Onychomycosis of the Feet

Treatment with Griseofulvin

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• **Griseofulvin, a new orally administered antifungal antibiotic which has proved to be effective for the treatment of a wide variety of superficial fungus infections of man, was used in the treatment of 51 patients with infections of the toenails due to *T. rubrum*. Thirty-four of the patients were treated with griseofulvin alone and seven were treated with griseofulvin combined with surgical avulsion of all involved toenails. The remaining ten had bilateral infections, and avulsion was done on one foot but not the other before griseofulvin therapy was begun.**

Of 34 patients who were treated with griseofulvin alone, few had complete cure even after prolonged treatment. Some nails showed improvement for a time, then no further gain; some showed no improvement; some showed resistant wedges of infection which penetrated proximally toward the posterior nail fold.

In the instances of surgical avulsion, clinically normal nails regrew during griseofulvin therapy. This simple procedure, with thorough removal of all underlying keratinous debris, apparently did away with foci of possible reinfection.

The results of the study indicated that surgical avulsion of the toenails in combination with griseofulvin therapy is an effective and practical method of treating onychomycosis of the toenails due to *T. rubrum*.

GRISEOFULVIN, a recently introduced orally administered antifungal antibiotic, has been demonstrated to be an extremely effective agent for the treatment of a wide variety of superficial fungus infections of man. The drug was first isolated by Oxford and coworkers[17] in 1939 from *Penicillium griseofulvum* (Dierckx). It is a colorless crystalline neutral compound with an empirical formula of $C_{17}H_{17}O_6Cl$. In vitro studies demonstrated griseofulvin to be fungistatic for a wide variety of fungi pathogenic for man, animals and plants,[1,4,5,6,8] and early investigation was concerned with its possible use as a fungicide in agriculture.[5,6]

Gentles, in 1958[10] demonstrated the effectiveness of orally administered griseofulvin for the treatment of experimentally induced ringworm in guinea pigs. This stimulated great interest in griseofulvin as a possible agent for the treatment of fungus infections in man. Early studies demonstrating the favorable effect of griseofulvin on superficial fungus infections were reported by Riehl,[18,19] Williams and coworkers,[27] and Blank and Roth.[4] These preliminary findings were confirmed by many subsequent investigators.* The essence of these reports is that griseofulvin is at present the treatment of choice in the management of tinea capitis due to a wide variety of organisms, and when properly used has been uniformly successful in achieving cure in all instances recorded to date. It has also favorably influenced the course of the common fungus infections of the palms, soles and nails except for moniliasis and is effective against the majority of fungus infections of the glabrous skin except for tinea versicolor, erythrasma and moniliasis. It is not effective against bacteria or any of the more common systemic diseases caused by fungi. Two possible exceptions appear to be the diseases caused by *Sporotrichum schenkii* and *Nocardia brasiliensis*.[14,24]

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Therapy of onychomycosis of the fingernails has been in general satisfactory when doses in the range of 1 gram daily are given. However, the response of toenails infected with *T. rubrum* has been in general disappointing. In our experience the majority of patients have not achieved cure even where therapy has been continued for almost a full year. In some instances all nails show evidence of initial improvement only to reach a plateau and then have no further improvement despite continued therapy. In others, initial improvement is followed by evidence of relapse characterized by the development of wedges of infected nail extending proximally toward the posterior nail fold. And in still other cases all but one or two nails may show improvement and eventually cure, while the disease in adjacent nails does not appear to respond at all.

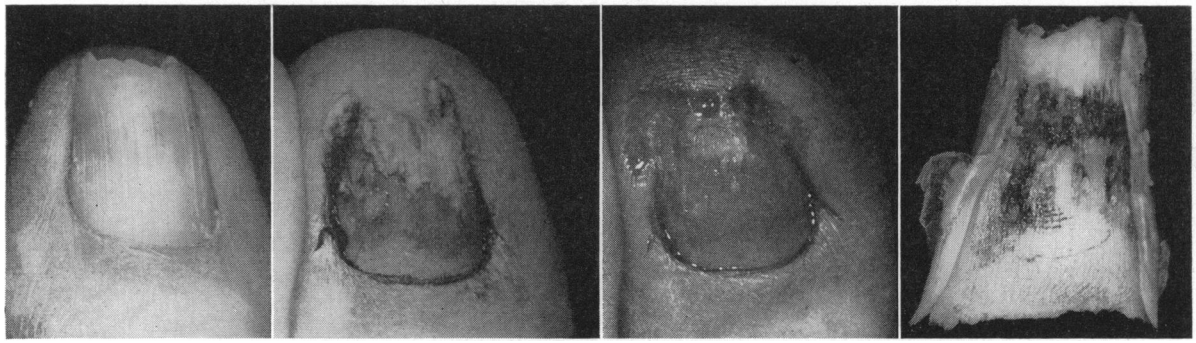

Figure 1.—Technique of surgical avulsion of toenails. *Left to right:* Large toenail before avulsion; nail bed immediately after avulsion of large toenail, with keratinous debris over surface of nail bed; nail bed after thorough removal of keratinous debris by curettage (the material was culturally positive for *T. rubrum*); and undersurface of avulsed nail, showing intact nail plate and keratinous debris clinging to undersurface.

These disturbing observations are particularly important in view of the fact that in the majority of cases of onychomycosis of the toenails in this country the infecting organism is *T. rubrum*. In addition, residually infected toenails obviously serve as foci of reinfection, and further relapses appear inevitable upon discontinuation of therapy. It seems, therefore, highly desirable to employ any adjuvant measures which will increase the probability of achieving complete cure of the disease in all the toenails.

In the treatment of tinea capitis with griseofulvin, it soon became obvious that clipping off the infected portions of the hair and applying topical fungicides were extremely effective adjuvant measures. This was on the basis that griseofulvin is fungistatic not fungicidal and that infected tissue which is not shed or destroyed harbors viable organisms.[16]

The extremely slow and erratic growth of the toenails together with the large accumulation of subungual keratinous debris which may be present provides a situation in which surgical avulsion of the nail plate and thorough curettage of the associated keratinous debris would appear to be highly desirable. The purpose of this paper is to report the value of the surgical removal of infected toenails and associated keratinous debris as adjuvants to griseofulvin therapy of onychomycosis of the toenails due to *T. rubrum*.

MATERIALS AND METHODS

Fifty-one patients with onychomycosis of the toenails were studied. In all cases the infecting organism was proven by culture to be *T. rubrum*. The patients were divided into three groups. Those in Group I, consisting of 34 patients, were treated with griseofulvin alone in dosages varying from 1 gm. weekly to 1 gm. daily for periods of from 14 to 339 days. Group II consisted of seven patients, in whom all involved nails were surgically avulsed before or shortly after the beginning of griseofulvin therapy. These patients received griseofulvin in dosages of from 1 gm. twice weekly to 1 gm. daily for periods of from 23 to 203 days. Group III consisted of ten patients with *T. rubrum* infection of the toenails of both feet. In each of these patients the nails of one foot were surgically avulsed before griseofulvin therapy was begun, while the nails of the other foot were left untouched. These patients received griseofulvin in doses of from 1 gm. twice weekly to 1 gm. daily for periods ranging from 78 days to 269 days.

TABLE 1.—*Average Time In Days to Achieve Percentage Regrowth*

	Group I	Group II
Total patients	34	7
Proportion of regrowth (stated as per cent):		
0 to 24 per cent..	41 days (7-111)	23 days (23)
25 to 49 per cent..	80 days (40-117)	.....
50 to 74 per cent..	145 days (65-225)	91 days (90-92)
75 to 99 per cent..	239 days (111-339)	160 days (118-202)
100 per cent.....	161 days (96-211)	176 days (150-203)

Note: Figures in parentheses indicate range of number of days from which average is derived.

Group I: Patients treated with oral griseofulvin alone.

Group II: Patients treated with oral griseofulvin plus surgical avulsion of all infected nails.

Surgical avulsion was performed under local nerve block anesthesia with 1 or 2 per cent lidocaine (Xylocaine®). After the nail was freed by blunt and sharp dissection from the posterior and lateral nail folds and the underlying nail bed, it was removed by firm traction. The underlying nail bed and especially the lateral gutters beneath the lateral nail folds were thoroughly curetted to remove all residual keratinous debris, care being taken to avoid damaging the matrix. The steps in this procedure are illustrated in Figure 1, which also shows the significant amount of potentially infectious keratinous debris which remains even after complete avulsion of the nail plate. Culture of the debris in this case was positive for *T. rubrum*.

Patients were observed at weekly or bi-weekly intervals and careful records, including photographs in many cases, were kept of the regrowth of new normal nails, as well as of any evidence of relapse or resistance to therapy.

RESULTS

In comparing the results of the treatment of patients in Group I with those of Group II (see Table 1) it was evident that the time necessary to achieve a given proportion of regrowth was in general less in those patients in whom the toenails had been surgically avulsed, in addition to receiving griseofulvin orally, than in those who received griseofulvin alone. A great individual variation in the rate of nail growth was observed.

In Group III the individual variation between patients was not a factor, since the 10 patients had *T. rubrum* infections of the toenails of both feet but surgical avulsion of the nails on only one foot, the other foot serving as a control. All patients received griseofulvin orally within one week after the surgical removal of the toenails on one foot. The results obtained in the individual patients studied in this manner are summarized in Table 2, and the rate of regrowth of normal nails in each of the two feet is presented in Table 3.

In all patients studied in this manner to date the regrowth of new normal nail at any given time was

TABLE 2.—*Comparison of Avulsed with Nonavulsed Nails in the Treatment of Onychomycosis with Griseofulvin*

Case No.	Age	Sex	Race	Duration of Infection	Dose	Frequency	Duration of Therapy	Total Dose	Results		Comments
									Avulsed	Nonavulsed	
1.	40	F	W	10 years	1 gm.	d	126 d	126 gm.	75% regrowth of normal nail	30% regrowth of normal nail	Still being treated
2.	42	F	W	20 years	1 gm.	d	87 d	87 gm.	Small nails 90% regrowth; large toenail 70% regrowth	Less than 10% regrowth	Some of the nonavulsed nails show streaks of infection almost to posterior nailfold. Still being treated.
3.	35	F	W	Many years	1 gm. 1 gm.	d qod	71 d 35 d	88 gm.	70% regrowth of normal nail	30% regrowth of normal nail	Some of the nonavulsed nails show streaks of infection almost to posterior nailfold. Still being treated.
4.	46	F	W	20 years	1 gm. 1 gm. 1 gm.	biw tiw d	133 d 27 d 108 d	158 gm.	Toenails 100% regrowth; fingernails 100% regrowth	Toenails 50% regrowth; fingernails 80% regrowth	Still being treated
5.	52	F	W	10 years	1 gm. 1 gm. 1 gm.	d biw tiw	21 d 76 d 182 d	111 gm.	100% regrowth of normal nail at 78 days	75% regrowth at 78 days; 90% regrowth at 233 days	At 233 days, previously nonavulsed nails surgically removed. 56 days later they showed 50% new nail growth. Still being treated.
6.	42	F	W	Many years	1 gm. 1 gm.	d qod	29 d 63 d	61 gm.	Small toenails 90% regrowth; large toenail 60% regrowth	Small toenails 75% regrowth; large toenail 20% regrowth	Still being treated
7.	31	F	W	2 years	1 gm.	d	78 d	78 gm.	50% regrowth normal nail	30% regrowth normal nail	Still being treated
8.	28	M	Mex	Many years	1 gm.	d	82 d	82 gm.	Small nails 95% regrowth; large nail 50% regrowth	Small nails 20% regrowth; large nail less than 10%	Still being treated
9.	43	F	W	Many years	1 gm.	d	50 d	50 gm.	Large toenail 30% regrowth; small toenails 50% regrowth	Large toenail 10% regrowth; small toenails 20% regrowth	Still being treated
10.	50	M	W	15 years	1 gm. 1 gm. 1 gm. 1 gm. 1 gm.	biw d biw tiw d	52 d 21 d 63 d 56 d 107 d	185 gm.	100% regrowth at 215 days	40% regrowth at 215 days; 50% regrowth at 269 days	Still being treated

Abbreviations: d=daily; biw=twice weekly; tiw=3 times weekly; qod=every other day.

faster on the toes on which avulsion was done (Table 4).

Not only did the nonavulsed nails fail to regrow as rapidly but in several instances they showed areas of resistant infection extending deep into the apparently new normal nail growth. The problem of persistent infection with resistant areas within the nail is well illustrated by the case of a 28-year-old white man, with a 6-year history of infection with *T. rubrum*. After 215 days of therapy with orally administered griseofulvin alone, resistant tongues of infection could still be seen in the first toe of the left foot extending deeply toward the nail base (Figure 2). The nail was then surgically avulsed and the patient subsequently received griseofulvin 1 gm. daily for 28 days. Then he was outside our observation for five months and received no treatment in that time. When he returned, it was observed that the nail had entirely regrown. The regrowth was new, normal nail, uniform throughout the nail plate, and there was no evidence of resistant areas or reinfection although griseofulvin therapy had been discontinued five months before.

In general, the small toenails show a greater proportional regrowth at a given time than do the toenails of the first toe. Actual measurements, however, indicate that the number of millimeters of regrowth is approximately the same as measured from the posterior nail fold to the free end of the nail and that the proportional difference results from the fact that the large toenail is longer than the smaller toenails.

TABLE 3.—*Average Time in Days to Achieve Percentage Regrowth*

	Group III	
	Avulsed	Nonavulsed
Total patients	10	10
0 to 24 per cent....	....	....
25 to 49 per cent..	50 days (50)	100 days (78-126)
50 to 74 per cent..	81 days (78-106)	255 days (241-269)
75 to 99 per cent..	97 days (82-126)	163 days (92-233)
100 per cent.....	177 days (78-241)	.....

Group III: Patients with bilateral toenail infections due to *T. rubrum*. In each patient all toenails on one foot surgically avulsed and nails of other foot remained as control.

TABLE 4.—*Comparison of the Percentage Regrowth of Avulsed vs. Nonavulsed Toenails (Group III) at the Time of This Study*

Patient	Duration of Treatment	Percentage Regrowth		Difference Percentage Points
		Avulsed	Nonavulsed	
1.	126 days	75	30	45
2.	87 days	90—S* 70—L*	10—S&L	80—S 60—L
3.	106 days	70	30	40
4.	268 days	100	50	50
5.	78 days	100	75	25
6.	92 days	90—S 60—L	75—S 20—L	15—S 40—L
7.	78 days	50	30	20
8.	82 days	95—S 50—L	20—S 10—L	75—S 40—L
9.	50 days	50—S 30—L	20—S 10—L	30—S 20—L
10.	215 days	100	40	60

*S—Small toenails.
*L—Large toenails.

DISCUSSION

Accumulated clinical evidence concerning the use of griseofulvin in the treatment of onychomycosis of the toenails due to *T. rubrum* indicates that griseofulvin alone is not effective in completely eradicating these infections. Only three of the thirty-four patients in the present series who were treated with griseofulvin alone had reached clinical cure at the time of compilation of the data for this study. Although many of these patients had not yet been treated long enough for a complete cure to be expected, among those who had been treated for such a period, and in whom a definite indication of the final outcome could be determined, there tended to be several clinical patterns: (1) Early improvement followed by apparent arrest of the progress of improvement despite continued adequate griseofulvin therapy; (2) early improvement followed by the development in one or more nails of clinical relapse characterized by progressive, deeply extending wedges of infection; and (3) improvement in the majority of diseased nails even to the point of complete clinical cure, yet complete or partial failure of response of one or more nails.

The importance of this problem cannot be overemphasized from the epidemiological standpoint, since in well over 90 per cent of the patients with onychomycosis that we have encountered to date, the infecting organism was *T. rubrum*. Further, from the standpoint of prognosis for the individual patient, the remaining foci of infection most certainly constitute a constant threat of reinfection and the development of new lesions upon discontinuance of therapy.

The fact that griseofulvin has not been found to eradicate the disease in the majority of patients treated to date may be attributed to one or more of several factors:

1. The slow and erratic growth of toenails certainly must play an important role in determining the clinical response to the disease. It is estimated that the rate of growth of normal, uninfected toenails is such that they are totally replaced in from six to nine months, but no data are available with respect to the rate of growth of severely diseased nails. It is our clinical impression that infection with *T. rubrum* may in some instances inhibit the rate of growth of the toenails.

2. It has been demonstrated that griseofulvin is actually deposited in hair[11] and the stratum corneum[24] in sufficient amounts to act as a fungistatic agent. Of great clinical importance was the finding that griseofulvin could not be detected in more than minimal amounts in the outer 20 per cent of the stratum corneum,[24] and this might in part account for the persistence of infection and the development of relapses in some instances of *T. rubrum* infection of the palms and soles. The pattern of distribution of griseofulvin in the toenails, the amounts present, the location within the nail and the persistence in situ after initial deposition is unknown, but will most likely prove to be extremely important in de-

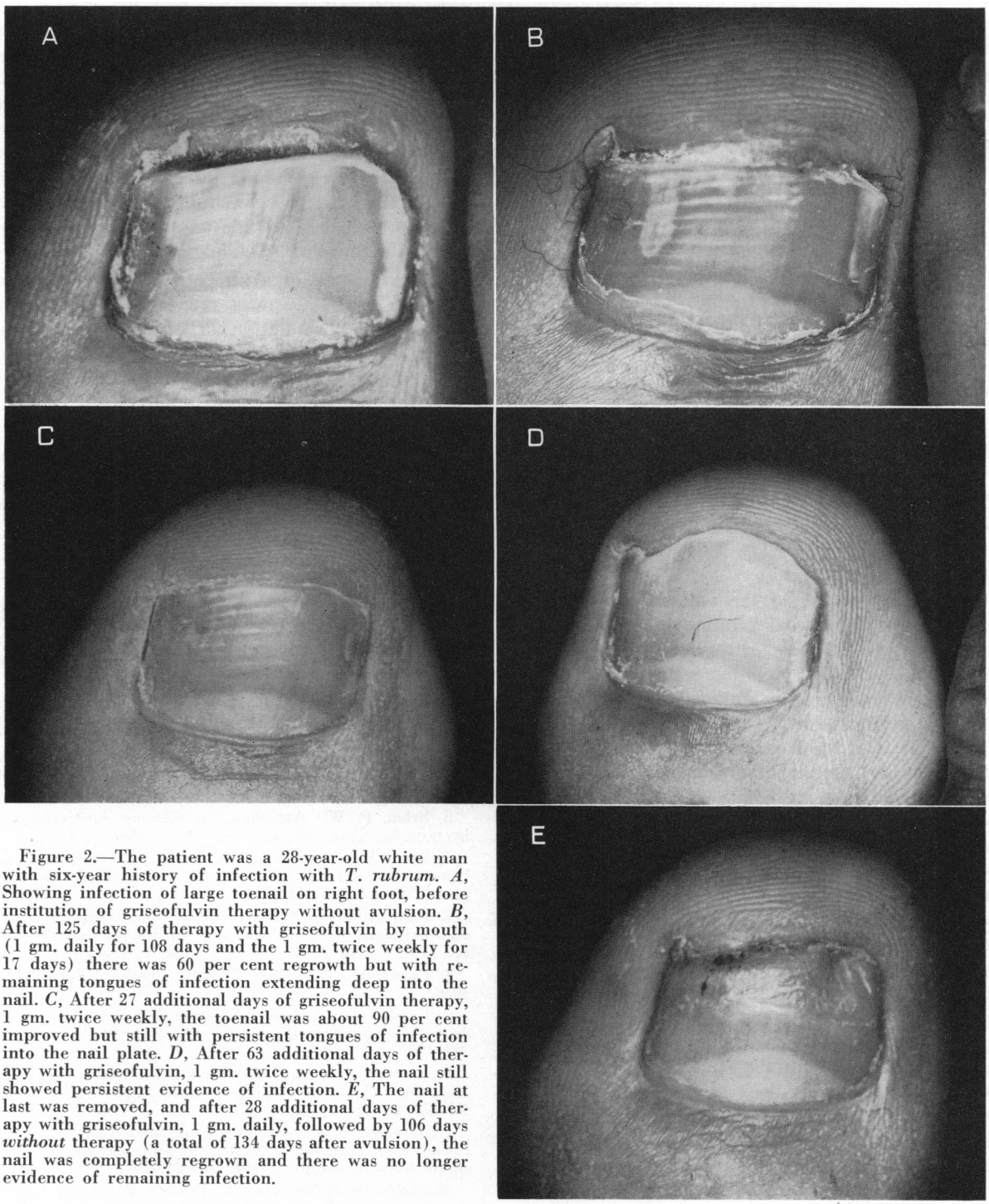

Figure 2.—The patient was a 28-year-old white man with six-year history of infection with *T. rubrum*. *A*, Showing infection of large toenail on right foot, before institution of griseofulvin therapy without avulsion. *B*, After 125 days of therapy with griseofulvin by mouth (1 gm. daily for 108 days and the 1 gm. twice weekly for 17 days) there was 60 per cent regrowth but with remaining tongues of infection extending deep into the nail. *C*, After 27 additional days of griseofulvin therapy, 1 gm. twice weekly, the toenail was about 90 per cent improved but still with persistent tongues of infection into the nail plate. *D*, After 63 additional days of therapy with griseofulvin, 1 gm. twice weekly, the nail still showed persistent evidence of infection. *E*, The nail at last was removed, and after 28 additional days of therapy with griseofulvin, 1 gm. daily, followed by 106 days *without* therapy (a total of 134 days after avulsion), the nail was completely regrown and there was no longer evidence of remaining infection.

termining the rate of cure. One of the theories explaining the inability to detect griseofulvin in the upper layers of the stratum corneum is that it is perhaps destroyed by bacteria and other organisms. This same possibility exists in toenails that are severely infected and deformed.

3. Although *T. rubrum* plays a major and vital role in initiating these infections, the large accumulations of subungual debris are rapidly colonized by other fungi and bacteria. Possibly these organisms have synergistic effect in perpetuating *T. rubrum* infections, or perhaps they have a role in inactivating griseofulvin.

4. Although an increased tolerance to the drug has been demonstrated *in vitro* this has not been encountered clinically to date.[20,21,22] Still it looms as a possibility in such chronic infections as onychomycosis of the toenails.

5. Other factors, including degree of sweating, occupation, frequency of bathing, use of dusting powder, type of shoes and the frequency of changing shoes and socks are extremely important variables which in the susceptible individual may play a critical role.

6. A peculiar susceptibility involving a unique defect in the host resistance may be postulated as the major factor involved in the inability to achieve complete cure. There is not yet enough data on patients with complete cure and long observation afterward to permit a conclusion as to that hypothesis.

Surgical avulsion of the nail and complete removal of all subungual keratinous debris was considered as an adjuvant of therapy for the purpose of accelerating cure and increasing the incidence of cure in patients with *T. rubrum* infection of the toenails treated with griseofulvin. This was mainly on the basis of the fact that in some instances cure has followed carefully performed surgical avulsion of the nails alone. In addition, it was felt that the operation would mechanically remove a potential source of reinfection at the outset of therapy. Results of the present study strongly support the concept that surgical avulsion of the toenails provides a valuable adjuvant to griseofulvin therapy. In comparing those patients who underwent surgical avulsion of the toenails before or concomitant with griseofulvin therapy (Group II) with those who received griseofulvin alone (Group I) certain clinical impressions stood out clearly. First, the new nails all appeared at essentially the same time and appeared to grow at essentially the same rate. The small toenail regrew in approximately three to four months, but apparently a much longer time was required for the large toenail. The nails appeared firm throughout with no evidence of persistent foci of infection visible. No arrest in the progress toward cure was noted in toes from which the nail had been removed.

The variability of rate of regrowth of the nails among the patients in these two groups was of such a nature that the exact value of the procedure upon rate of return of normal nails could not be determined accurately. However, in the third group of patients who had bilateral onychomycosis but avulsion of the nails on only one foot, the effect of this procedure was unquestionable. In all instances, the nails returned at a more rapid rate on the foot on which avulsion had been performed.

The avulsion procedure was well tolerated by the patients, resulting in disability for only one to three days even when all the nails were avulsed on the same day. The moderate discomfort and time involved appeared to be well justified by the better results obtained with this adjuvant to the recommended regimen of griseofulvin therapy.

The technique of avulsing is of paramount importance. Not only must the entire nail plate be removed, but in addition all keratinous debris underlying the plate must be thoroughly curetted from the nail bed and from beneath the lateral nail folds to remove all possible foci of reinfection.

Finally, it should also be stressed that this procedure does not supplant the necessity for adhering to the traditional basic principles of foot hygiene.

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